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GUEST EDITORIAL

Do the Newer Imaging Modalities Affect Management of Solid Tumors?

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POSITRON EMISSION TOMOGRAPHY

Positron emission tomography (PET) utilizes the glucose analog [2] [18F]fluoro-2-deoxy-D-glucose (FDG) to enter the cell's metabolic cycle. The FDG cannot be further metabolized and is trapped in the cell, permitting imaging. The more rapid the cell turnover, the greater the FDG accumulation [1]. Although the familiar cross-sectional anatomic imagine seen with the computerized axial tomography (CT) scan is not present with PET, the advantages of whole body image and tumor-specific metabolic information are gained. Solid tumor systems that have been successfully scanned include colorectal, breast, lung, head and neck, melanoma, lymphoma, thyroid and musculoskeletal cancers [2].

There are a number of clinical oncologic applications of PET imaging. These include (1) more complete staging of primary tumors; (2) differentiating residual or recurrent tumor from scar or radiation necrosis in previously operated or irradiated sites; (3) characterizing enlarged lymph nodes as malignant and detecting malignancy in normal-sized lymph nodes; (4) detecting tumor site(s) when conventional imaging modalities are negative or equivocal and symptoms, signs, or elevated tumor markers indicate recurrence; (5) predicting efficacy of treatment as a function of concentration and metabolic activity of FDG; and (6) monitoring the response of tumor to treatment over time [3].

Multiple studies confirm sensitivities and specificities of near 90% and 100%, respectively [4]. Very few false positive scans are recorded. The confounding lesions include acute inflammation, chronic pancreatitis, retroperitoneal fibrosis, and salivary gland tumors [5].

In a recent European report, Belgian researchers retrospectively reviewed 103 patients with suspected recurrent colorectal cancer. Comparison of FDG-PET was made to conventional staging, carcinoembryonic angiten (CEA), endoscopy, CT scans of the chest, abdomen, and pelvis, magnetic resonance imaging (MRI), and ultrasound. FDG-PET was more accurate than the conventional diagnostic modalities and had a significant impact on patient management [6]. The advantage of whole body screening in one examination and the detection of unsuspected metastatic sites were noted.

The superiority of PET over CT scan was demonstrated in both pelvic recurrences: PET detected 81% of the metastatic sites, whereas CT scan identified 59%. Similarly, in the liver, PET detected 96% of metastasis, slightly better than the 90% by CT scan. The sensitivity of retroperitoneal lymph node involvement was similar for both modalities at 73% detection. Neither imaging system efficiently identified peritoneal involvement, an area of metastatic disease that is uniquely detected by monoclonal antibody (MAb) scanning.

Importantly, patient management decisions are altered by upstaging (17% of operable cases) and downstaging (9%) of the recurrent colorectal cases. A particularly strong application of FDG-PET is in the subset of patients with elevated serum CEA and negative or equivocal conventional staging who have recurrent disease. In the Belgian study with 9 such patients, FDG-PET correctly detected the site(s) of relapse in 5 and excluded disease in 2 patients.

A significant application of FDG-PET in recurrent colorectal cancer is to detect extrahepatic disease before proposed curative liver resection. In a Frankfurt study of 36 patients with liver metastasis, PET led to a change in management in 39% of patients [7]. The most evident impact is in avoiding noncurative surgery in patients with previously undetected multiple extrahepatic metastases.

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TABLE I. Alternative Algorithm for Suspected Recurrent, Metastatic, or Occult Colorectal Cancer and Rising CEA

Conventional	Alternative
Colonoscopy	PET imaging
Chest radiograph	Focused work-up
CT chest/abdomen/pelvis	
Serial CEA	
Bone scan	

An important issue is cost-effectiveness in the application of PET in oncology. Studies on non–small cell lung cancer, recurrent colorectal cancer, metastatic melanoma, and staging of advanced head and neck and Hodgkin disease all demonstrated more accurate detection and extent of nonresectable disease with PET imaging. Importantly, operations for noncurable disease or CT scan abnormalities (PET negative) were avoided by utilizing the information gained by PET scan. Significant cost savings are realized by obviating nontherapeutic interventions, justifying the $1,800 expense of PET imaging [8]. An example of an alternative algorithm is demonstrated in the patient with rising CEA levels and recurrent colorectal cancer (Table I). Given the 89% positive predictive value and 100% negative predictable value in recurrent colorectal cancer, it is reasonable to go directly to PET imaging and reserve conventional scanning work-up for these patients who demonstrate a positive FDG-PET scan [4].

In a recent study in Buffalo (NY), we evaluated 20 patients with solitary liver metastasis (by CT and MRI criteria) from colorectal cancer origin. The PET scan demonstrated additional disease in 12 of the 20 patients: 6 with extrahepatic metastases and 6 patients with bilobar, multiple liver metastases. In 9 of the 12 additional disease patients, no operation was undertaken. Disease confirmation was obtained by percutaneous biopsy. The remaining 3 patients required laparotomy to confirm the extrahepatic disease. In none of the 12 additional disease patients was a liver resection performed. This small study illustrates the decision-making impact PET scanning can have on therapeutic and cost-saving strategies.

Initial Health Care Financing Administration (HCFA) approval of Medicare reimbursement for the evaluation of solitary pulmonary nodule and the staging of non–small lung cancer was granted in January 1998. In July 1999, coverage was expanded to include recurrent colorectal cancer, staging of lymphoma (Hodgkin and non-Hodgkin disease), and recurrent melanoma (Table 2).

RADIOIMMUNOSCINTIGRAPHY

In recent years, radiolabeled MAbs directed against tumor- associated antigens have been introduced to stage more thoroughly primary solid malignancies and to identify recurrent or metastatic disease. The technique of radioimmunoscintigraphy has been effectively employed to aid oncologic decision- making in colorectal cancer. When liver resection is being contemplated for solitary metastasis, the MAb scan is utilized to rule out extrahepatic, extra-abdominal, or locoregional recurrence before surgery is undertaken [9]. Similarly, when pelvic or other locoregional recurrence is identified, the immunoscintigraphy (IS) is obtained to confirm the recurrence and rule out synchronous parenchymal (liver, lung, adrenal, brain) or bone metastasis. Finally, the origin of a rising tumor marker and negative conventional work-up can be ascertained with MAb imaging in 80% of instances [10]. Identification of occult disease, confirmation of disseminated or additional disease, and accurate direction of surgery to truly isolated liver/lung metastasis or local recurrent disease can impact therapeutic decision-making and alter management in up to 55% of patients [11]. When compared to cross-sectional and PET imaging, the unique niche of IS is in the detection of peritoneal disease, which is readily confirmed by laparoscopy or percutaneous biopsy.

One of the drawbacks to the original murine MAbs was the human anti-mouse antibody response following injection. Strategies to offset this phenomenon include use of fragments (Fab^1) or totally humanized MAb. In a multicenter report of patient management benefit employing HumaSpect-Tc, a totally human MAb, Wolff et al. [12] found this imaging to be more accurate than CT in determining disease resectability in recurrent, metastatic, or occult colorectal cancer.

A more recent application of this technology was in the diagnosis of breast carcinoma. CEA IS has been employed as an adjunctive test in women with abnormal mammograms who had palpable and nonpalpable breast lesions. One hundred seventy-nine women underwent scintigraphic imaging with an antibody Fab^1 fragment labeled with ^{99m}Tc. A sensitivity of 82% and a specificity

TABLE II. HFCA Approval of Medicare Reimbursement for Oncologic PET Imaging

January 1, 1998	July 1, 1999
Solitary pulmonary nodule	Recurrent colorectal cancer (with rising levels of CEA)
Staging non–small cell lung cancer	Staging for lymphoma (Hodgkin and non-Hodgkin disease: PET must substitute for gallium scan)
	Recurrent melanoma

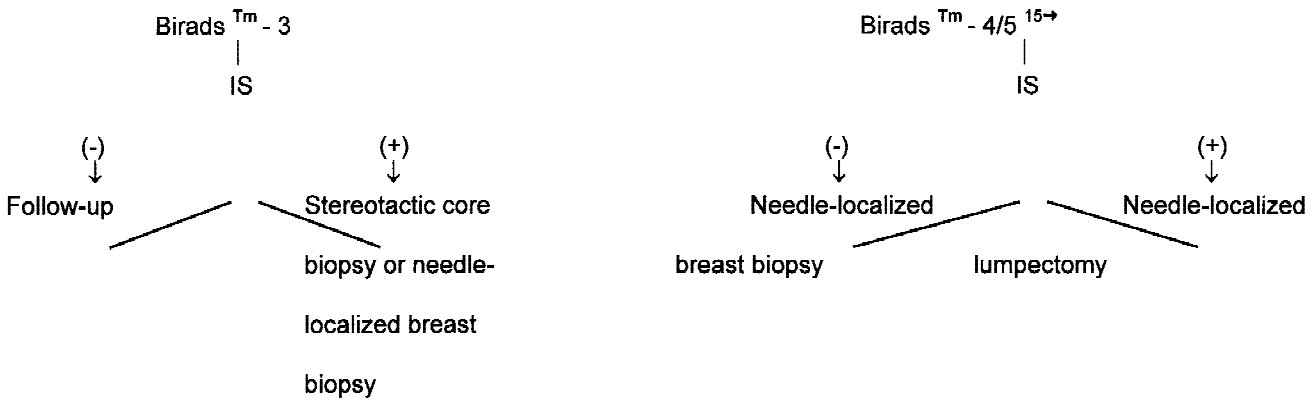

Fig. 1. Alternative algorithm employing IS for nonpalpable mammographic abnormality.

of 90% were found. The imaging agent was safe both in respect to adverse reactions and human anti-human antibody (HAHA) response. In the subset of 72 patients with nonpalpable and suspicious or indeterminate mammograms, IS was more accurate than mammography (88% vs. 72%) and had significantly ($P < 0.01$) higher specificity than mammography (97% vs. 75%) [13]. This test appears to complement the high sensitivity of screening mammography and has a higher specificity for differentiating benign from malignant lesions. In patients with breasts that are difficult to examine (dense, postoperative, postirradiated, implant containing, or reconstructed) or for whom the mammography is indeterminate, radioimmunoscintigraphy may determine when a biopsy should be performed or when cautious follow-up may be appropriate. True benefit from IS in the diagnosis of breast cancer would be realized if an invasive test (e.g., stereotactic core biopsy or needle-localized breast biopsy) could be eliminated or only follow-up recommended on the basis of a positive or negative MAb scan (Goldenberg et al., personal communciation). An alternative algorithm employing IS for a nonpalpable mammographic abnormality is presented in Figure 1.

The role of these newer imaging agents, PET and IS, in clinical oncology has yet to be defined. The niche areas where these modalities have demonstrated greater sensitivity and specificity must be explored to impact decision-making and cost-effectiveness. Focused comparative trials of cross-sectional vs. functional imaging, relative to patient outcome, must now be undertaken.

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